64. The composition of Claim 1, wherein the heparin or heparin-like compound is non-covalently attached to the peptide.

65. The composition of Claim 1 wherein the substrate is selected from the group comprising fibrin, collagen and synthetic polymer hydrogels.

Remarks

The following comments are in response to rejections made in the parent application in view of the prior art.

Rejection Under 35 U.S.C. § 103

Claims 1, 3-6, 20, 24-27, and 60-66 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Schroeder-Tefft et al., *J. Controlled Release* 48:29-33 (1997) (Schroeder-Tefft) in view of Kwon et al., *J. Controlled Release* 22: 83-94 (1992) (Kwon), Cardin & Weintraub, *Arteriosclerosis* 9:1 (21-32) (1989) (Cardin), Darling & Fahnestock, *Biochemistry* 27:6686-6692 (1988) (Darling), DeBlois et al., *Biomaterials* 15:9 (665-672) (1992) (DeBlois), and Powell et al., *Brain Research* 515: 309-311 (1990) (Powell).

Claims 21 and 26 were rejected under 35 U.S.C. § 103(a) as being obvious over Schroeder-Tefft in view of Kwon, Cardin, Darling, DeBlois, and Powell and in further view of Alberts et al., *Molecular Biology of the Cell* (1994) (Alberts).

Claims 57 and 58 were rejected under 35 U.S.C. § 103(a) as being obvious over Schroeder-Tefft in view of Kwon, Cardin, Darling, DeBlois, and Powell and in further view of Levi-Montalcini et al., *TINS* 19:11 (514-520) (1996) (Levi-Montalcini).

The present invention

The present invention is related to the controlled delivery of growth factors, which bind to heparin or heparin-like compounds with **low affinity – i.e., they are "non-heparin binding-growth factors**. The claims are directed to compositions, specific uses for the compositions and methods for delivering these growth factors. The controlled delivery compositions contain a substrate, a peptide with a domain the binds with heparin or heparin-like compounds with high affinity, heparin or a heparin-like compound, and a growth factor that binds with heparin with low affinity. The high-affinity peptide is **covalently** attached to the substrate. In turn, heparin or heparin-like compounds bind to the peptide and are immobilized on the substrate, either by covalent bonds or non-covalent bonds (see e.g. Example 3, at page 17, lines 14-18). Non-heparin binding peptides are then loosely associated with the heparin and released upon use.

Schroeder-Tefft

Schroeder-Tefft does not teach or suggest grafting heparin to a collagen substrate to create a composition for the controlled delivery of growth factors. In fact, Schroeder-Tefft *teaches away* from grafting heparin to a substrate. Schroeder-Tefft teaches that TGF-β2 should be complexed to heparin, and then the heparin/TGF-β2 complex should be **mixed** with collagen (see page 295, col. 1). Since collagen also binds with heparin, this order, i.e. first binding the heparin to TGF-β2 (in the absence of collagen), **prevents** the binding of heparin with collagen and maximizes the binding of heparin with TGF-β2. Further, nowhere does Schroeder-Tefft teach or suggest that the drug delivery composition should include a peptide which links to heparin (or a heparin-like compound), as required by the claims. Schroeder-Tefft specifically

uses a tight binding of heparin to the substance to be released, to stabilize the protein; not to release it.

Kwon

Kwon is directed at studying the viability of using ion exchange as a release mechanism for macromolecular delivery from microspheres (page 84, col. 1). Kwon neither teaches nor suggests covalently binding a peptide to a substrate with heparin binding sites. Further, Kwon neither teaches nor suggests including a peptide with heparin binding domains to help deliver a growth factor with a domain that binds with heparin with low affinity.

Cardin

Cardin identifies heparin binding regions in proteins.

Darling

Darling is directed at determining the biological role of the different subunits of NGF. Nowhere does Darling teach or suggest the claimed compositions, uses or methods for delivery of growth factors that bind heparin with low affinity.

DeBlois

DeBlois is directed at the delivery of FGF, a heparin-binding growth factor (see page 665, col. 2). It does not teach or suggest compositions or methods for the delivery of growth factors that bind to heparin with low affinity.

Powell

Powell controlled release of NGF from ethylene-vinyl acetate copolymer (EVAc) implants that contain NGF. Powell does not teach or suggest that release of a growth factor with

a domain that bind to heparin with low affinity can be controlled through the use of a substrate and a peptide, which contains heparin binding domains.

Alberts

Alberts is directed to a general discussion of glycosaminoglycans.

Levi-Montalcini

Levi-Montalcini provides a general disclosure of NGF's role in the nervous, immune and endocrine systems.

The combined references

Even if these references were combined, they would not teach or suggest the claims compositions, uses for the compositions, or methods to one of ordinary skill in the art. None of these references teaches binding heparin to a substrate. In fact, Schroeder-Tefft teaches away from binding heparin with the substrate, by emphasizing the importance of the order of first binding heparin to TGF-β2 and subsequently mixing the heparin/ TGF-β2 complex with the substrate. Nor do these references teach or suggest that the using a substrate, a peptide with a domain the binds with heparin or heparin-like compounds, heparin or a heparin-like compound, and a growth factor that binds with heparin with low affinity will provide for the controlled release of the growth factor.

Allowance of claims 1, 3-16, 18-27, 57-59, and 61-65, as amended, is respectfully solicited.

Respectfully submitted,

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: May 3, 2001

Marked Up Version of Amended Specification Paragraphs

Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)

Page 1, first paragraph, insert –This is a continuation of U.S. Serial No. 09/298,084 filed April 22, 1999, now abandoned.--

Please amend the paragraph on page 6, lines 13-19 as follows.

The peptides of the invention that bind heparin with high affinity have a characteristic amino acid domain that will not elute from a heparin-affinity column at less than 140 mM NaCl. While many potential peptides exist, the inventors have identified several peptide sequences in particular. These are exemplified in the amino acid sequences identified in [SEQ. ID. NO.: 1, SEQ ID. NO.: 2, SEQ ID. NO.: 3, SEQ ID. NO.: 4, and SEQ ID. NO.: 5] <u>SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5</u>. Many other peptides may be used apart from the specifically enumerated sequences here.

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